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CLINICAL STUDY

Relationship between red cell distribution width and mean platelet volume with new onset atrial fibrillation after off-pump coronary artery bypass grafting

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ABSTRACT

OBJECTIVE: The aim of this study was to evaluate the relationship between red blood cell distribution width (RDW) and mean platelet volume (MPV) with development of postoperative atrial fibrillation (PoAF) after off-pump coronary artery bypass grafting (CABG).

BACKGROUND: The RDW and MPV have been associated with some cardiovascular disorders.

METHODS: A total of 93 patients who underwent off-pump CABG were included in this study. The patients were divided into two groups as developing and nondeveloping PoAF groups in the postoperative period. We measured whether RDW and MPV levels are a predictive value for development PoAF.

RESULTS: There were 24 patients with PoAF enrolled (mean age: 66 ± 7.8 years) and 69 patients without PoAF (mean age: 56.26 ± 11.53 years). The PoAF was significantly correlated with age (p = 0.004), hematocrit (p: 0.010), RDW (p = 0.007) and creatinine (p = 0.006). Only advanced age (p = 0.012) was identified as an independent predictor of PoAF. For predicting PoAF, there was 79.2 % sensitivity and 65.2 % specificity for RDW (p = 0.001) and 62.5 % sensitivity and 55.1 % specificity for MPV (p = 0.062).

CONCLUSIONS: We found that RDW levels and MPV were not an independent predictor of the development of PoAF. However, elevated RDW levels and MPV may be one of the predictive values for PoAF development *(Tab. 3, Fig. 2, Ref. 27).* Text in PDF *www.elis.sk.*

KEY WORDS: red blood cell, mean platelet volume, atrial fibrillation, coronary artery bypass, off-pump.

Introduction

After coronary artery bypass grafting surgery (CABG), atrial fibrillation (AF) may occur as a common complication (1). Postoperative atrial fibrillation (PoAF) has a high prevalence, affecting 20 to 45 % of CABG (2). Atrial fibrillation frequently occurs in the first five days of the postoperative period and peaks between 24 and 72 hours. It becomes uncommon after the first week (2). PoAF has been associated with an increase in early and late mortality rates, hospital adverse events, particularly hemodynamic instability, thromboembolic events and heart failure progression.

Intraoperative factors can be consequent upon cardiac ischemia and inflammation due to the complexity of the surgical procedure. The CABG with cardiopulmonary bypass seems to have a higher incidence for PoAF as compared with off-pump CABG (2).

The red blood cell distribution width (RDW) is a test showing the change in size or volume of erythrocytes. It is expected that the sizes of erythrocytes produced in the bone marrow are close to each other. It is not normal if there are differences between the sizes. Increases of RDW levels are correlated with inflammatory markers and are accepted as a sign of ineffective erythropoiesis which occurs in critically ill patients (3). In the last decade, studies have been carried out on prognostic marker on RDW in various cardiovascular disorders besides blood diseases. Many studies have shown that RDW is a strong predictor of adverse outcomes in patients with heart failure, stroke and myocardial infarction (4–6). In previous studies, in patients undergoing coronary angiography and CABG indicated a possible association between RDW and AF (7, 8).

The mean platelet volume (MPV) is one of the most important biomarkers of platelet activity. Activated platelets have larger volumes and contain wide range of vasoactive substances and prothrombotic factors. Therefore, MPV may also be a response to inflammation and thrombosis (9). An increased MPV is associated with overall cerebrovascular and cardiovascular mortality rates (10).

The red blood cell distribution width and MPV have been associated with some cardiovascular disorders, but the relationship with AF is still uncertain. However, the relation between the RDW and MPV levels and PoAF has not been researched in patients undergoing off-pump coronary artery bypass grafting. We aimed to

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investigate the relation between the RDW and MPV levels with PoAF in these patients.

Materials and methods

Patients

This retrospective observational study included 114 consecutive patients who underwent off-pump CABG between 2014 and 2017 at the Department of Cardiovascular Surgery, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey. The study was approved by the local institutional Ethical Committee of University of Health Sciences.

All data to be analyzed retrospectively were retrieved from the hospital medical files. The exclusion criteria were preoperative AF or flutter, previous treatment with amiodarone, presence of valvular heart disease, chronic obstructive pulmonary disease (COPD), prolonged intensive care unit (ICU) stay, redo cardiac surgery, bleeding revision, chronic renal failure. Six patients with COPD, 2 patients with chronic renal failure, 7 patients with moderate mitral valve disease, 2 patients with preoperative AF, 2 patients with previous cardiac surgery history, 1 patient with postoperative bleeding and 1 patient with prolonged ICU stay were excluded. Thus, the remaining 93 patients with off-pump CABG were included in the study.

All data were recorded as age, gender, history of hypertension, diabetes mellitus, preoperative drug use (beta-blockers, statins, ACE or ARB inhibitors), ejection fraction, left atrial diameter, body mass index, body surface area, Euroscore, number of anastomoses, postoperative bleeding amount, duration of ICU stay, and discharge time from hospital.

Laboratory measurements

Fasting blood samples were drawn from an antecubital vein of each patient before operation. The tubes with EDTA were used for automatic blood count according to the protocol of our hospital. Complete blood cell count include parameters such as red blood cell count, hematocrit, hemoglobin, red cell distribution withd, mean corpuscular volume, total white blood cell count, neutrophil and lymphocyte counts, platelet count and mean platelet volume. These parametres were measured by using an automated hematological analyzer (Coulter LH 780 Analyzer, CA, USA). The complete blood cell parameters were measured through Coulter Erythrolyse II Reagent Kit (Beckman Coulter, Ireland). The reference range for RDW was 11.5–14.0 %, reference range for MPV was 6.96–10.13 %.

Diagnosis of PoAF

The patients were monitored in ICU with continous heart rhythm and invasive blood pressure monitoring. In addition, a 12-lead electrocardiographic recordings (ECG) were also obtained daily during in the ICU. Patients were monitored continuously by five-lead telemetry in the regular ward. When the patients complained of palpitation, dyspnea and angina, 12-lead ECG was taken. Postoperative AF was described as irregular, fast oscillations, or fibrillatory waves instead of regular P waves at ECG. An AF episode lasting longer than 5 minutes was accepted as PoAF. Standard medical cardioversion treatment was conducted with amiodarone (5 mg/kg) for 30 minutes, followed by 900 mg/day.

Statistical analysis

Statistical analysis data were analyzed with the Statistical Package for the Social Sciences (IBM SPSS Statistic Inc. version 21.0, Chicago, IL, USA).Continuous and ordinal variables were expressed as mean ± standard deviation and nominal variables were expressed as frequency and percentage. Kolmogorov–Smirnov test and Shapiro–Wilk tests of normality were used to identify distribution of variables. Student's t test was used to compare two groups for continuous variables with normal distribution.Chi Square test was used to compare two groups for nominal variables. Mann–Whitney U test was used to compare two groups for continuous variables without normal distribution. The relationship between the preoperative independent variables and the development of PoAF was evaluated by a binary logistic regression analysis. For all tests, a $p < 0.05$ was considered statistically significant. Receiver-operating characteristic (ROC) curve was applied for the prediction of PoAF after off-pump CABG and the area under the curve was calculated for RDW and MPV levels.

Results

A total number of 24 patients in the PoAF(+) group (66.7 % male, mean age: 66 ± 7.8 years) and 69 patients in the PoAF(–) group (72.5 % male, mean age: 56.26 ± 11.53 years) were enrolled in to the study. The demographic and clinical properties of the subjects are summarized in Table 1. Both PoAF(+) group and PoAF(–) group were similar to each other with regard to demographic characteristics. However, there was statistical difference between two group in terms of age ($p = 0.000$) (Tab. 1).

The comparisons of laboratory and operative parameters are shown in Table 2. Significant differences were observed between two groups in terms of hematocrit, RDW, blood urea nitrogen

Tab. 1. Demographic features of patients.

	PoAF(–) group n=69	PoAF (+) group n=24	p*
Age (years)	56.26±11.53	66±7.8	0.000#
Male gender, n (%)	50 (72.5)	16 (66.7)	0.590*
Hypertension, n (%)	32 (46.4)	15 (62.5)	0.174*
Diabetes mellitus, n (%)	29 (42)	6 (25)	0.138*
CAD, n (%)	10 (14.5)	6 (25)	0.240*
PAD, n (%)	5 (7.2)	3 (12.5)	0.429*
Preoperatif MI, n (%)	19 (27.5)	5 (20.8)	0.518*
Beta-blocker therapy, n (%)	65 (92.8)	21 (87.5)	0.429*
Statin therapy, n (%)	47 (68.1)	18 (75)	0.527*
ACE-I/ARB therapy, n (%)	29 (56.5)	14 (58.3)	0.609*
EuroSCORE II	2.77±1.88	3.67±1.9	0.054a
Number of anastomosis	1.35±0.56 (1–3)	1.63±0.71 (1–3)	0.067a
BSA	1.87±0.17	1.83±0.14	0.265#
BMI	27.31±4.51	27.47±4.2	0.735a

PoAF – Postoperative atrial fibrillation, CAD – Carotid artery disease, PAD – Peripheral artery disease, ACE-I – Angiotensin-converting enzyme inhibitor, ARB – Angiotensin-receptor blocker, BSA – Body surface area, BMI – Body mass index. * Pearson Chi- Suquare, # Student's *t* test, a Mann–Whitney U test.

Tab. 2. Laboratory and operative variables.

	PoAF (–) group n=69	PoAF (+) group n=24	p*
Hematocrit (%)	41.16±3.47	38.83±3.36	**0.001**[a]
White blood cell (10^3/μL)	9.01±2.2	9.12±2.39	0.846[#]
Platelet (10^3/μL)	249.36±72.76	248.17±86.7	0.871[a]
Red cell distribution width (%)	13.63±1.17	14.52±1.3	**0.001**[a]
Mean platelet volume (fL)	8.72±0.77	9.03±0.84	0.061[a]
BUN (mg/dL)	17.43±6.86	22.12±7.88	**0.004**[a]
Creatinine (mg/dL)	0.84±0.23	1.01±0.24	**0.004**[a]
Na (mEq/L)	139.16±2.57	138.88±2.36	0.635[a]
K (mEq/L)	4.05±0.68	4.12±0.39	0.724[a]
Ca (mg/dl)	9.24±0.46	9.01±0.52	0.069[#]
Mg (mg/dl)	1.9±0.22	1.89±0.16	0.813[#]
Free T_3 (pg/mL)	3.03±0.44	2.86±0.3	0.136[a]
Free T_4 (ng/dL)	1.15±0.21	1.09±0.17	0.169[#]
TSH (IU/mL)	3.29±5.42	2.33±1.33	0.909[a]
C Reactive protein (mg/dL)	10.33±17.52	12.57±21.77	0.287[a]
Total Cholesterol(mg/dl)	196.49±34.86	198.67±30.35	0.787[#]
LDL-C (mg/dl)	121.94±31.57	125.55±26.88	0.618[#]
HDL-C (mg/dl)	40.7±5.96	43.07±9.89	0.306[a]
TG (mg/dl)	171.96±75.2	141.71±56.88	0.075[a]
Ejection fraction (%)	48.91±11.37	47.92±9.31	0.538[a]
Left atrium diameter (mm)	37.81±3.9	38.46±4.58	0.650[a]
Postoperative bleeding (ml)	597.1±233.08	620±213.03	0.644[a]
ICU stay (day)	2.14±0.43	2.79±0.77	**0.000**[a]
Hospital stay (day)	6.01±0.93	7.25±1.26	**0.000**[a]

PoAF – Postoperative atrial fibrillation, ICU – Intensive care unit. [#]Student's-t test, [a] Mann–Whitney U test.

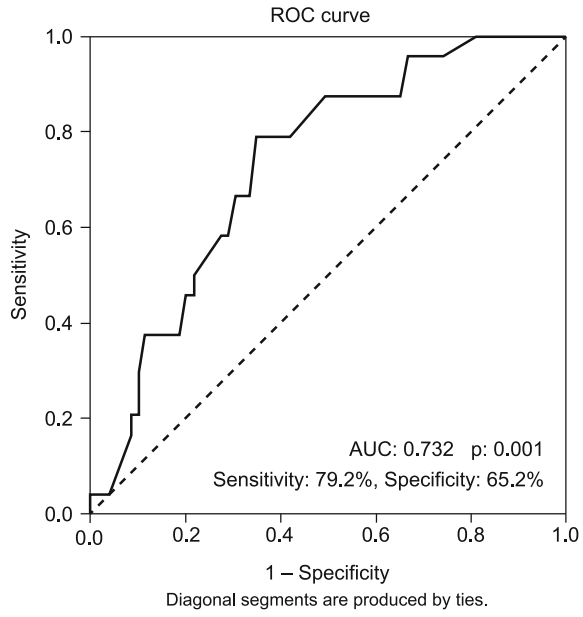

Fig. 1. ROC curve and AUC for RDW for predicting PoAF. ROC – Receiver operation characteristic, AUC – Area under the curve, RDW – Red cell distribution witdh, PoAF – Postoperative atrial fibrillation.

(BUN), creatinin, ICU stay and hospital stay. There were statistical differences between the two groups in terms of hematocrit, RDW, BUN, creatinin, ICU stay and hospital stay as a negative affect to PoAF(+) group (p = 0.001, p = 0.001, p = 0.004, p = 0.004, p = 0.000 and p = 0.000, respectively) (Tab. 2). In addition, ejection fraction, left atrium diameter and MPV level were not significantly different between the groups (p = 0.538, p = 0.650 and p = 0.061 respectively) (Tab. 2).

Risk factors related to the development of PoAF were included in the univariate logistic regression analysis. In unadjusted univariate logistic regression analysis, the PoAF was significantly correlated with age (OR [Odds Ratio]: 1.083, 95 % CI [Confidence interval]: 1.025–1.144, p = 0.004), hematocrit (OR: 0.829, 95 % CI: 0.720–0.956, p = 0.010), RDW (OR: 1.740, 95 % CI: 1.166–2.598, p = 0.007), BUN (OR: 1.084, 95 % CI: 1.018–1.154, p = 0.011) and creatinine (OR: 16.313, 95 % CI: 2.193–121.333, p = 0.006) but was not correlated with hypertension, diabetes mellitus, ejection fraction, left atrium diameter, EuroSCORE II and MPV (Tab. 3). Only age was identified as an independent predictor of development AF after off-pump CABG surgery in multivariate analysis (OR: 1.074, 95 % CI: 1.016–1.135, p = 0.012) (Tab. 3).

Additionally, in ROC curve analysis, it was determined a cut-off level of 13.65 for RDW for predicting PoAF (Area under the curve (AUC): 0.732, 95 % CI: 0.625–0.840, Log rank p = 0.001)

Tab. 3. Binary Logistic regression analysis to identify predictors of PoAF.

Variables	Univariate analysis			Multivariate analysis		
	p	Exp(B) Odds Ratio	95 % C.I. Lower Upper	p	Exp(B) Odds Ratio	95 % C.I. Lower Upper
Age	0.001	1.089	1.306 – 1.145	0.012	1.074	1.016 – 1.135
HT	0.177	.519	.200 – 1.345			
DM	0.143	2.175	.769 – 6.155			
EF	0.697	.992	.950 – 1.035			
LAD	0.502	1.041	.926 – 1.171			
EuroSCORE II	0.054	1.274	.996 – 1.629			
Hct	0.010	.829	.720 – .956	0.125	.866	.721 – 1.041
RDW	0.007	1.740	1.166 – 2.598	0.094	1.519	.931 – 2.479
MPV	0.103	1.603	.909 – 2.824			
BUN	0.011	1.084	1.018 – 1.154	0.214	1.062	.966 – 1.168
Creatinine	0.006	16.313	2.193 – 121.333	0.475	3.009	.147 – 61.792

PoAF – Postoperative atrial fibrillation, , HT; Hypertension, DM; Diabetes mellitus, EF; Ejection fraction, LAD; Left atrium diameter, RDW – Red cell distribution, MPV – Mean platelet volume, Hct – Hematocrit

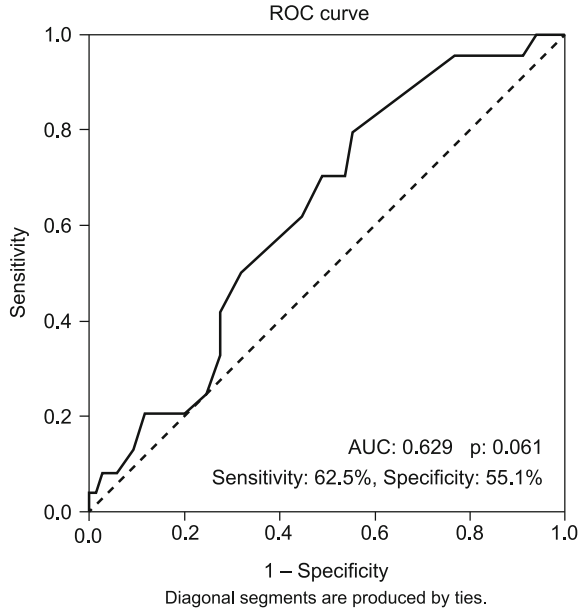

Fig. 2. ROC curve and AUC for MPV for predicting PoAF. ROC – Receiver operation characteristic, AUC – Area under the curve, MPV – Mean platelet volume, PoAF – Postoperative atrial fibrillation.

(Fig. 1). For MPV, it was determined as a cut-off level of 8.75 for predicting PoAF (AUC: 0.629, 95 % CI: 0.508–0.749, Log rank p = 0.062) (Fig. 2). For predicting PoAF, in the measurements above their cut-off values, there was 79.2 % sensitivity and 65.2 % specificity for RDW and 62.5 % sensitivity and 55.1 % specificity for MPV.

Discussion

In our study, we assessed the effect of RDW and MPV levels in the development of PoAF in patients undergoing off-pump CABG. In univariate logistic regression analysis, we found that advanced age, lower hematocrit levels, higher RDW, higher BUN and creatinine levels were significantly correlated with the development of PoAF. In multivariate logistic regression analysis, only advanced age was detected as an independent predictor for the development of POAF. In addition, in the measurements above cut-off value, there was 79.2 % sensitivity and 65.2 % specificity for predicting PoAF for RDW (AUC: 0.732, Log rank p: 0.001), 62.5 % sensitivity and 55.1 % specificity for MPV (AUC: 0.629, Log rank p: 0.062). But in our study, RDW and MPV were not independent predictors for the development of PoAF.

The incidence of PoAF following CABG surgery is seen in 25–40 % of cases (2). However, its frequency reaches 62 % following combined CABG and valve surgery (11). Previous study demonstrated that patients with mitral regurgitation were more likely to experience recurrent AF post-ablation (12). Therefore, we excluded 7 patients with moderate mitral valve disease so that it is not effecting the outcome of the study.

There has been an increased risk of new-onset AF in patients with COPD. Mathew et al (13) have showed that COPD increased the incidence of both persistent and paroxysmal AF and the incidence of PoAF increased to 43 % in the presence of COPD. Negative prognostic effect of atrial fibrillation has been demonstrated in COPD patients. For this reason, patients with COPD were excluded in order to have more accurate results.

Chronic renal disease is associated with the risk of multiple life threatening complications and AF is common in this group of patients. In the large population-based study, Alonso et al (14) reported that reduced renal function and presence of albuminuria were strongly associated with the incidence of AF independently of other risk factors. Similar to these studies, in our study, higher BUN and higher creatinine levels were statistically significant in patients with PoAF. In addition, BUN and creatinine levels were significantly correlated with the development of PoAF in univariate logistic regression analysis. Our study showed once again a relationship between reduced renal function and AF.

In our study, both in univariate logistic regression analysis and in multivariate logistic regression analysis, we found that only age significantly correlated with the development of PoAF. Advanced age was detected as an independent predictor of the development of AF in our study. Age-related changes, including atrial fibrosis and accumulation of amyloid, can cause intraatrial reentry, which leads to the development of AF (15). Age has been repeatedly shown to be the major risk factor for AF after cardiac surgery (16,17). Our results were generally consistent with the literature . When the age is considered as a risk factor, it is known that elder patients have high risk for developing AF.

In the last decade, studies have been carried out on prognostic marker of RDW in various cardiovascular disorders besides blood diseases. A variety of mechanisms have been proposed for the association between RDW levels and cardiovascular outcomes. Oxidative stress and chronic inflammation may reduce survival of erythrocytes leading to a more mixed population of erythrocyte volumes in circulation (18, 19). In acute and chronic cardiovascular diseases, inflammatory cytokines and neurohumoral mediators are activated. Inflammatory cytokines have been found to suppress the maturation of erythrocytes, so the increased immature erythrocytes may reflect higher RDW values (19). It has been reported that an exaggerated inflammatory response is associated with a higher risk of PoAF (20). Previous studies have demonstrated that RDW is independently associated with both AF and postoperative new-onset AF following elective cardiac surgery with a high sensitivity and specificity (21, 22). In a systematic review with meta-analysis, mean RDW was 15.03 % in the PoAF(+) group and 14.62 % in the PoAF(–) group and the meta analysis showed that RDW was significantly higher in the PoAF(+) group as a positive predictor ($p < 0.001$) (23). In a previous study, Eryd et al (21) demonstrated that high RDW values were associated with the development of paroxysmal AF. Gungor et al (24) reported that RDW is an independent marker of non-valvular AF in multivariate logistic regression analysis (OR: 4.18, 95 % CI 2.15–8.15, p = 0.01). In one of the first studies to investigate the relationship between RDW and PoAF in patients undergoing CABG, Ertas et al (8) found that

while preoperative RDW levels were significantly higher in patients who developed AF, there was not any correlation between postoperative RDW levels and AF. In addition, they remarked that preoperative RDW level predicts new-onset AF after CABG in patients without histories of AF(cutpoint of 13.45, 61 % sensitivity, 60 % specificity) (8). Likewise, we think that postoperative RDW value can not be associated with atrial fibrillation after CABG due to possible bleeding, hypoxia, and inotropic agent use. Therefore, we assessed only preoperative RDW values. In our study, we found that RDW levels were significantly higher in the PoAF(+) group ($p = 0.001$). Also, in our study, in univariate logistic regression analysis we found that higher RDW levels were correlated with the development of PoAF (OR: 1.740, 95 % CI: 1.166–2.598, $p = 0.007$). But, RDW levels were not an independent predictor for the development of PoAF. For predicting PoAF above cut-off level of 13.65 of RDW , in ROC curve analysis, we found that there was 79.2 % sensitivity and 65.2 % specificity (AUC: 0.732, 95 % CI: 0.625–0.840, Log rank $p = 0.001$) (Fig. 1). There is no study indicating the relationship between the RDW levels and PoAF in patients undergoing isolated off-pump CABG. Therefore, the results of our study may take into consideration relationship between high RDW levels and postoperative AF.

Activated platelets have larger volumes and contain wide range of vasoactive substances and prothrombotic factors. Therefore, MPV may also be a response to inflammation and thrombosis (9). It has been reported that an exaggerated inflammatory response is associated with a higher risk of PoAF (20). An increased MPV is associated with overall cerebrovascular and cardiovascular mortality rates (10). Previous studies have shown the association of MPV with thrombotic events (9), slow coronary flow (25) and left atrial stasis (10) in patients with AF. In a systematic review with meta-analysis, mean of MPV was 9.35 femtolitre(fl) in the PoAF(+) group and 9.05 fl in the PoAF(–) group and the meta analysis showed that MPV was significantly higher in the PoAF(+) group as a positive predictor ($p < 0.001$) (23). In a study evaluating the relationship between serum laboratory parameters and new onset atrial fibrillation, Karatas et al.(26) found that increased levels of CRP, MPV, RDW, uric acid and neutrophil to lymphocyte ratio independently predicted new onset AF. In previous study to investigate the relationship between MPV and PoAF in patients undergoing CABG, Erdem et al (27) found that MPV was significantly higher in the AF group ($p < 0.001$) and in multivariate logistic regression analysis showed that MPV were independent predictors of PoAF (95 % CI: 1.326–4.958, p: 0.005). In addition, they remarked their results show that increased platelet activity is associated with the development of AF after CABG. In our study, we found that MPV was not significantly higher in the PoAF(+) group ($p = 0.061$). In addition, in univariate logistic regression analysis we found that higher MPV was not correlated with the development of PoAF ($p = 0.103$). Therefore, MPV was not an independent predictor for the development of PoAF. But, in ROC curve analysis, we found that there was 62.5 % sensitivity and 55.1 % specificity for MPV (AUC: 0.629, Log rank $p = 0.062$) (Fig. 2). We think that our AUC value is not a bad value for MPV. But there is a need for further work in this issue.

In our study, it provided homogeneity between the groups, because we excluded the risk factors such as COPD and valvular heart diseases for developing AF. Therefore, the results of our study may be more specific in terms of the relationship between raised RDW level and raised MPV with PoAF.

Conclusion

There is no study on the relationship between the MPV and PoAF in patients undergoing isolated off-pump CABG. Many factors contribute to the development of AF after coronary bypass surgery. Many studies have been done on PoAF development. RDW levels may be a predictor of postoperative complications such as AF. As a result of this study, we thought that high RDW level could be a factor of the development of PoAF and there is a need for further work for MPV. We think that these factors should be taken into account before surgery.

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